pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone of about 20 pg*hr/ml to about 31 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T_{max}) of estrone of about 4 hrs to about 8 hrs.

In some embodiments, a pessary provided herein comprises about 10 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estrone sulfate of about 10 pg/ml to about 16 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone sulfate of about 56 pg*hr/ml to about 84 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T_{max}) of estrone sulfate of about 4 hrs to about 7 hrs.

In some embodiments, a pessary provided herein comprises about 4 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estradiol of about 4 pg/ml to about 8 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estradiol of about 16 pg*hr/ml to about 26 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T_{max}) of estradiol of about 0.25 hrs to about 2 hrs.

In some embodiments, a pessary provided herein comprises about 4 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estrone of about 1 pg/ml to about 3 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone of about 8 pg*hr/ml to about 13 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T_{max}) of estrone of about 1 hrs to about 4 hrs.

In some embodiments, a pessary provided herein comprises about 4 μg of estradiol, wherein administration of the pessary to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estrone sulfate of about 4 pg/ml to about 7 pg/ml; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone sulfate of about 22 pg*hr/ml to about 34 pg*hr/ml. In some embodiments, the pessary further provides a corrected geometric mean time to peak plasma concentration (T_{max}) of estrone sulfate of about 1 hrs to about 3 hrs.

Also provided herein is a pessary comprising about 1 μg to about 25 μg of estradiol, wherein administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C_{max}) of estradiol that is less than about 30 pg/ml. For example, administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C_{max}) of estradiol that is less than about 18 pg/ml.

In some embodiments, a pessary comprising about 1 μg to about 25 μg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estradiol that is less than about 112 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estradiol that is less than about 63 pg*hr/ml.

In some embodiments, a pessary comprising about 1 μg to about 25 μg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C_{max}) of estrone that is less than about 14 pg/ml. For example, administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C_{max}) of estrone that is less than about 7 pg/ml.

In some embodiments, a pessary comprising about 1 μg to about 25 μg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone that is less than about 65 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone that is less than about 31 pg*hr/ml.

In some embodiments, a pessary comprising about 1 μg to about 25 μg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C_{max}) of estrone sulfate that is less than about 613 pg/ml. For example, administration of the pessary to a patient provides a corrected geometric mean peak plasma concentration (C_{max}) of estrone sulfate that is less than about 16 pg/ml.

In some embodiments, a pessary comprising about 1 μg to about 25 μg of estradiol is provided, wherein administration of the pessary to a patient provides a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone sulfate that is less than about 5291 pg*hr/ml. For example, administration of the pessary to a patient provides a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone sulfate that is less than about 84 pg*hr/ml.

Further provided herein is a pessary comprising about 1 μg to about 25 μg of estradiol, wherein administration of the pessary to the proximal region of the vagina of a patient provides a therapeutically effective concentration of estradiol over 24 hours in the proximal region of the vagina.

This disclosure also provides a method of treating an estrogen-deficient state, the method comprising administering to a patient in need thereof, a pessary as provided herein. In some embodiments, a method of treating vulvovaginal atrophy is provided, the method comprising administering to a patient in need thereof, a pessary as provided herein.

In some embodiments of the methods provided herein, treatment comprises reducing the severity of one or more symptoms selected from the group consisting of: vaginal dryness, dyspareunia, vaginal or vulvar irritation, vaginal or vulvar burning, vaginal or vulvar itching, dysuria, and vaginal bleeding associated with sexual activity.

In some embodiments of the methods provided herein treatment comprises reducing the vaginal pH of the patient. For example, treatment comprises reducing the vaginal pH of the patient to a pH of less than about 5.0.

In some embodiments of the methods provided herein treatment comprises a change in cell composition of the patient. For example, the change in cell composition comprises reducing the number of parabasal vaginal cells or increasing the number of superficial vaginal cells. In some embodiments, the number of parabasal vaginal cells in the patient are reduced by at least about 35% (e.g., at least about 50%). In some embodiments, the number of superficial vaginal cells are increased by at least about 5% (e.g., at least about 35%).

Further provided herein is a method for reducing vaginal discharge following administration of a pessary, the method comprising administering to a patient in need thereof, a pessary provided herein, wherein the vaginal discharge following administration of the pessary is compared to the vaginal discharge following administration of a reference drug.